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Lymphocyte Predominant Hodgkin Disease: Clinico-Pathologic Features and Results of Treatment—The Pediatric Oncology Group Experience

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Purpose. In this report, the Pediatric Oncology Group (POG) experience with lymphocyte predominant Hodgkin Disease (LPHD) in children is reviewed.

Materials and Methods. From 1984–1993, the POG conducted 3 clinical trials for advanced stage HD and 2 for early stage HD. There were 26 cases of LPHD in 613 patients in these trials. Patients' ages ranged from 3.1–17.8 years (mean of 12.9 years). There was a marked male predominance.

Results. Histologic subtypes were 17 nodular, 8 diffuse pattern; 1 was indeterminant. The sites involved at diagnosis were primarily the peripheral lymph nodes. Fourteen patients had stage (S) I disease; 9 had SII; 3 had SIII; there was no SIV disease. Only 4 of 26 patients had B symptoms. All 26 patients achieved complete remission, 10 with radiotherapy, 6 with chemotherapy and 10 with combined modality therapy. Treatment was not uniform since patients were registered on different protocols. Event-free survival after 5 years was 86.5 percent. Two patients developed and succumbed to large cell, T-cell type, non-Hodgkin lymphoma (NHL).

Conclusions. Optimal treatment for LPHD should focus on efforts to limit the risk of second malignancy. Med. Pediatr. Oncol. 29:519–525, 1997.

Key words: Hodgkin disease; lymphocyte

INTRODUCTION

In 1966 Lukes and Butler [1] proposed a classification of Hodgkin Disease (HD) in which the grouping lymphocyte predominant was the combination of the previous nodular and diffuse lymphocytic and histiocytic type of HD. LPHD has been considered a unified, biologically indolent entity in which 90% of patients presented in low clinical stage (I and II) and had excellent long-term outcomes [2,3]. LPHD also is associated with a unimodal age distribution [4], marked male predominance [5], and frequent axillary presentation [5,6]. The nodular and diffuse variants of LPHD have similar clinical characteristics and relapse patterns. In addition, there is good immunological evidence that LPHD, particularly the nodular type, is of B-cell origin [7–9] and it has been reported to behave like low-grade, NHL, with an indolent clinical course and late recurrences [10,11]. Although patients with LPHD have an indolent clinical course, some studies have shown they have an increased risk for subsequent development of high-grade, NHL which is unrelated to therapy for LPHD [6]. In this report, the Pediatric Oncology Group (POG) experience with LPHD in children is reviewed.

MATERIALS AND METHODS

From 1984–1993, the POG conducted 3 clinical trials for advanced stage HD and 2 for early stage HD (Table I). There were 26 cases of LPHD in 613 patients in these trials.

Pathology

Histology was reviewed centrally by one of the authors (FGB). All cases fulfilled the diagnostic criteria for LPHD established by Lukes and Butler [1]. Hematoxylin and eosin stained biopsy sections from cases of LPHD, were subclassified as nodular or diffuse lymphocyte predominance subtypes. The diagnosis of nodular subtype

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TABLE I. POG Clinical Trials for Hodgkin Disease

Advanced stage (IIB/III2A/IIIB/IV)
- POG 8426-Pilot[12]
  - Staging laparotomy was required.
  - Four monthly cycles of MOPP alternating 4 monthly cycles of ABVD; followed by TN-RT (2,100 cGy) or modified TN-RT (pelvis omitted for patients without pelvic disease).
- POG 8725[13]
  - Staging laparotomy was optional.
  - Four monthly cycles of MOPP alternating 4 monthly cycles of ABVD; followed by TN-RT (2,100 cGy) vs no TN-RT.
- POG 9225-Pilot[14]
  - Staging laparotomy was optional.
  - Two monthly cycles of APPE followed by mantle RT (2,100 cGy); 2 monthly cycles of OPPA followed by abdominal RT including the spleen (2,100 cGY); one cycle of APPE followed by one cycle of OPPA; pelvic RT (for only positive pelvic nodes).

Early Stage (I/IIA/III1A)
- POG 8625[15]
  - Staging laparotomy was required.
  - Two monthly cycles of MOPP alternating 2 monthly cycles of ABVD followed by either cycles of MOPP/ABVD or IF-RT (2,500 cGy); or standard RT alone.
- POG 9226-Pilot[16]
  - Staging laparotomy was optional.
  - Four monthly cycles of ABVE followed by IF-RT (2,500 cGy).

MOPP: mechlorethamine, vincristine, procarbazine, prednisone; ABVD: doxorubicin, vinblastine, bleomycin, imidazole, carboximide; TN: total nodal; RT: radiotherapy; APPE: ara-C, cisplatin, prednisone, etoposide; OPPA: vincristine, prednisone, procarbazine; adriamycin; IF: involved field; ABVE: adriamycin, bleomycin, vincristine, etoposide.

required a pseudonodular effacement, without mature fibrosis, of the lymph node architecture by small or ''mature'' lymphocytes, occasional lymphocytic and histiocytic Hodgkin cells (L & H polyploid cells), and rare Reed-Sternberg cells. The subclassification of diffuse subtype required the predominance of small lymphocytes with or without lesser numbers of histiocytic cells, infrequent L & H polyploid cells, rare Reed-Sternberg cells, and an absence of a pseudonodular pattern and fibrosis. Biopsies with insufficient material to distinguish between nodular and diffuse subtypes were classified as ''lymphocyte predominance, indeterminant subtype.'' Initial diagnosis in all cases was confirmed by immunohistochemical studies. These were performed by a standard avidin-biotinylated enzyme complex assay using monoclonal antibodies to CD45, CD45 RO, CD20, CD30, and CD15 (Dako Corp., Carpinterid, CA).

Clinical

Clinical information for all 26 patients with LPHD was obtained from the POG data base and following data were tabulated: age, sex, initial site(s) of involvement, clinical stage (CS), pathological stage (PS), presence or absence of ''B'' symptoms, initial therapy and response, duration of follow up, recent status, and second malignancies. Written informed consent was obtained for all patients at the time of entry into one of the POG clinical trials.

RESULTS

The clinical characteristics, results of staging, histology, therapy, and outcome are presented in Table II. Patients' ages ranged from 3.1–17.8 years (mean 12.9 years). There was a marked male predominance (22 of 26 LPHD as compared to 355 of 613 for other subtypes; $P = 0.003$). The sites involved at diagnosis were primarily the peripheral lymph nodes: cervical (13), inguinal (8), submandibular (5), supraclavicular (5), iliac (5), axillary (4), and femoral (1) with several patients having more than one site. Other sites included mediastinal (2), spleen (2), hilar (1), and periaortic (1) nodes. Staging laparotomy was performed in 16 patients; none of the patients had a change from initial CS. Fourteen patients had stage I disease (7 CS, 7 PS); nine, stage II (2 CS, 7 PS); three stage III (2 CS, 1 PS); there was no stage IV disease. A statistically significant higher proportion of all POG early stage HD patients had LPHD than found in the advanced stage HD patients (23 of 294 early stage HD compared to 3 of 319 total advanced stage HD ($P < 0.001$). Only 4 of 26 patients had B symptoms. Of the four, one had stage I, one stage II, and two stage III. Three of these patients are in continuous complete remission (CCR) for 55, 25, and 71 months, respectively. One of the stage IIIB patients ($\neq$1), developed NHL after 39 months of follow up.

Seventeen of the 26 cases showed nodular and 8 cases showed diffuse pattern. One case was indeterminant because of a small size of the biopsy specimen.

All 26 patients achieved complete remission, 10 with radiotherapy (RT), 6 with chemotherapy (CT) and 10 with combined modality therapy (CMT). Treatment administered was not uniform since patients were registered on different protocols. The follow up period ranges from 25–87 months for the 23 patients in CCR. Event-

TABLE II. POG LPHD: Clinical Features, Histology, Staging, Therapy, and Outcome

Patient #	Protocol #	Age/Sex	Site(s) of presentation	Staging C/P	Histology	Therapy	Response	Duration (months)	Status
1	8426	10/M	R Axillary; L Inguinal	IIIB/–	N	CMT	CR	39	NHL; Died
2	8625	11/M	L Submandibular	IA/–	N	RT	CCR	31+	NED
3	8625	15/F	L Cervical	IA/IA	N	RT	CCR	38+	NED
4	8625	14/M	L Cervical; L Supraclavicular	IIA/IIA	N	RT	CCR	70+	NED
5	8625	15/M	L Cervical	IA/IA	D	RT	CCR	46+	NED
6	8625	15/M	R Cervical; R Supraclavicular	IIA/IIA	D	CMT	CCR	87+	NED
7	8625	18/M	R Axillary	IA/IA	D	RT	CCR	78+	NED
8	8625	18/M	R Iliac; R Femoral; R Inguinal	IIA/IIA	D	RT	CR	6	Relapsed; NHL; Died
9	8625	10/M	L Iliac; L Inguinal	IIA/IIA	N	CMT	CCR	67+	NED
10	8625	9/M	R/L Cervical; R/L Axillary; L Supraclavicular; Spleen	IIIA/IIIA	D	CMT	CCR	62+	NED
11	8625	12/F	R/L Submandibular; R Cervical; Mediastinum	IIA/IIA	N	CMT	CCR	51+	NED
12	8625	15/M	R Cervical	IA/IA	N	CT	CR	15	Relapsed; NED
13	8625	16/F	L Iliac; L Inguinal	IIA/IIA	N	RT	CCR	58+	NED
14	8625	17/M	L Supraclavicular	IA/IA	D	RT	CCR	59+	NED
15	8625	13/M	L Inguinal	IB/–	D	CT	CCR	55+	NED
16	8625	3/M	L Inguinal	IA/IA	D	CT	CCR	53+	NED
17	8625	11/M	R Iliac; R Inguinal	IIA/IIA	N	CMT	CCR	37+	NED
18	8625	13/M	L Inguinal	IA/–	N	CT	CCR	38+	NED
19	8625	6/F	L Submandibular	IA/–	N	CT	CCR	45+	NED
20	8625	9/M	L Cervical	IA/IA	N	CT	CCR	30+	NED
21	8625	17/M	R Axillary	IA/IA	N	RT	CCR	36+	NED
22	8725	13/M	R Cervical; R Hilar; Spleen; R Iliac; Retroperitoneal	IIIB/–	I	CMT	CCR	71+	NED
23	9225	15/M	R Submandibular; L Cervical; R Supraclavicular	IIB/–	N	CMT	CCR	25+	NED
24	9226	11/M	R Submandibular; L Cervical; Mediastinum	IIA/–	N	CMT	CCR	30+	NED
25	9226	8/M	R Cervical	IA/–	N	CMT	CCR	26+	NED
26	9226	14/M	R Cervical	IA/–	N	RT	CCR	28+	NED

C/P: Clinical/Pathological staging; N: Nodular; D: Diffuse; I: Indeterminant; M: Male; F: Female; R: Right; L: Left; CR: Complete remission; CCR: Continuous complete remission; CMT: Combined modality therapy; RT: Radiation therapy; CT: Chemotherapy; NHL: Non-Hodgkin lymphoma; NED: No evidence of disease

free survival (EFS) after five years was 86.5 percent with a standard error of 12 percent (Fig. 1).

Two patients had recurrences but neither were confirmed by surgical biopsy. One patient (≠12) with stage IA disease, nodular subtype, treated with chemotherapy alone (MOPP/ABVD × 3) relapsed in the local site 15 months post diagnosis. This patient is presently in remission with RT alone. The second patient (≠8) with stage IIA disease, diffuse subtype, treated with involved field RT alone had mediastinal relapse 6 months post diagnosis. Retreatment consisted of mantle RT. Forty months following the last treatment, this patient developed biopsy proven ''immunoblastic,'' large cell lymphoma (LCL), T-cell type, and died from progressive disease. A third patient (≠1) with stage IIIB disease treated with CMT (MOPP/ABVD × 4 and 2100 cGy total nodal radiation) developed biopsy proven LCL, T-cell type, 39 months after the diagnosis of HD and died from progressive disease. Thus, the only two deaths were from recognized second malignancies.

DISCUSSION

In this study there was marked male preponderance, greater than the 1.5–2.1:1 male:female ratio characteristic of HD in general [17,18]. The majority of patients

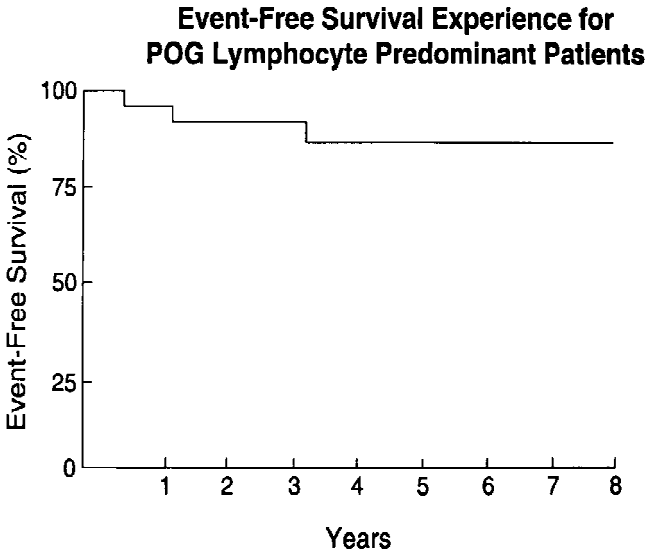

Fig. 1. Kaplan-Meier EFS curve of 26 patients with LPHD.

were asymptomatic and presented with localized disease. Although cervical or axillary nodes are the most common sites of presentation in LPHD [17,19,20], inguinal and femoral nodes were involved sites in 8 patients. Of the eight, seven had stage I or II infradiaphragmatic HD which is an unusual but known presentation [21–25]. Other clinical features in these patients included early stage and absent ''B'' symptoms.

This suggests that LPHD may be a distinct biological entity [26] which varies from the more common subtypes of HD.

Increased risk for developing secondary LCL in patients with LPHD, unrelated to primary therapy [4,6,7,32–35] and coexistence of LPHD with LCL have also been reported [6,27–31]. Frequency of subsequent NHL following LPHD is about 150-fold to that expected [6]. Most reported cases of secondary NHL in patients have been diffuse LCL. It has been suggested that the L & H cell, probably the neoplastic cell type in LPHD, is a variant of the immunoblast [36]. The British National Lymphoma Investigation experience over 20 years shows a 3.8% incidence of secondary NHL, diffuse large cell or mixed lymphoma in patients with LPHD [18]. In contrast, their 20 year overall incidence of NHL for the nodular sclerosing subtype and mixed cell group was 0.7% and 0.3% respectively. Recently, it has been suggested that there is a clonal relationship between LPHD and concurrent or subsequent LCL of B-lineage [37]. However, the LCLs that developed in our two patients were of T-cell type.

CONCLUSION

This small group of patients reveals that both nodular and diffuse LPHD have similar natural histories in terms of involved sites, stage, and constitutional symptomatology at presentation, which is quite different from other histologic types of childhood HD. This may suggest that LPHD is biologically closer to NHL than to other subtypes of HD. Given the risks of ''secondary'' NHL reported in the British National Lymphoma Study [18] and the fact that the only 2 deaths in our patients were from LCL, we suggest that therapy for LPHD in childhood be designed to minimize use of agents known to be associated with secondary malignancies in patients with HD. Prospective studies aimed at minimizing total treatment may help to determine the optimal approach to LPHD. Limited chemotherapy [38], low dose involved-field radiotherapy [39] or even observation of patients with no residual disease following surgery might be considered.

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APPENDIX

INSTITUTION	GRANT NO.
All Children's Hospital, St. Petersburgh, FL	
Baylor College of Medicine, Houston, TX	CA-03161
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Cancer Center of Hawaii, Honolulu, HI	
Carolinas Medical Center, Charlotte, NC	CA-69177
Children's Hospital and Health Center, San Diego, CA	CA-28439
Children's Hospital Greenville Health System, Greenville, SC	CA-69177
Children's Hospital of Michigan, Detroit, MI	CA-29691
Children's Hospital of New Orleans, LA	
Christ Hospital and Medical Center, Oak Lawn, IL	CA-07431
Cook-Ft. Worth Children's Medical Center, Ft. Worth, TX	CA-33625
Dartmouth-Hitchcock Medical Center, Lebanon, NH	CA-29293
Duke University, Durham, NC	CA-15525
East Carolina University School of Medicine, Greenville, NC	CA-69177
East Tennessee State University, Mountain Home, TN	CA-31566
Emory University School of Medicine, Atlanta, GA	CA-20549
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Hospital Saint-Justine, Montreal, Canada	
Hurley Medical Center, Flint, MI	CA-29691
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McGill University, Montreal, Canada	CA-33587
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POG Statistical Office, Gainesville, FL	CA-29139
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Scott & White Memorial Hospital, Temple, TX	CA-33625
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University of Mississippi Medical Center, Jackson, MS	CA-15989
University of Missouri, Columbia, MO	CA-05587
University of New Mexico, Albuquerque, NM	CA-11233
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University of Rochester Medical Center, Rochester, NY	
University of South Alabama, Mobile, AL	
University of Texas, San Antonio, TX	
University of Texas-Galveston, Galveston, TX	CA-03161
University of Texas-Southwestern Medical Center, Dallas, TX	CA-33625
University of Vermont College of Medicine, Burlington, VT	CA-29293
University of Virginia, Charlottesville, VA	
Walter Reed Army Medical Center, Washington, DC	
Warren Clinics, Inc., Tulsa, OK	CA-11233
Washington University School of Medicine, St. Louis, MO	CA-05587
West Virginia University Health Science Center, Charleston, WV	CA-15525
Yale University School of Medicine, New Haven, CT	CA-69428